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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,443	COURTY ET AL.	
	Examiner	Art Unit	
	PHUONG HUYNH	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 May 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-40* is/are pending in the application.

4a) Of the above claim(s) *23-26,31-34,38 and 39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20,21,27-29,35-37 and 40* is/are rejected.

7)☒ Claim(s) *22 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *5/30/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 20-40 are pending.

2. Claims 23-26, 31-34 and 38-39 are withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

3. Claims 20-22, 27-30, 35-37 and 40 drawn to a peptide comprising the sequence of amino acid selected from the sequence 13-39 of the HARP factor or the sequence 65-97 of the HARP factor, a pharmaceutical composition comprising said peptide and one or more pharmaceutically acceptable excipient, a method for preparing a medicament comprising adding said peptide to a pharmaceutically acceptable vehicle, are being acted upon in this Office Action.

4. In view of the amendment filed March 17, 2007, all objections and rejections are hereby withdrawn.

5. The following new grounds of objections and rejections are necessitated by the amendment filed March 17, 2008.

6. Claim 28 is objected to because abbreviation "ALK" should have been a full name where it first appears in the claim. Amending the claim "Anaplastic Lymphoma Kinase (ALK) would obviated this objection.

7. Claim 29 is objected to because the phrase "said **further** peptide" should have been "said peptide consisting of SEQ ID NO: 4" if it is meant to refer to the peptide in claim 28.

8. The disclosure is objected to because of the following informalities: (1) the word "inve ntors" at page 4. Line 29 is misspelled. It should have been "inventors". (2) the range of HARP peptide **13-39 and 65-97** at page 25 line 25 is consistent with the "HARP peptides **16-48**" at page 25, line 33 of the specification and also inconsistent with the Figure legend of FIG 1 on the X axis. FIG. 1 discloses HARP **16-42** and HARP **68-100**. Also, if FIG 1 is presume to be corrected, then the

sequence listing in paper copy and computer copy of the sequence listings are not corrected and vice versa. Appropriate correction is required.

9. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

10. Claim 37 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The "said second peptide" in claim 37 has no antecedent basis in base claim 35 because the phrase "second peptide" is not recite in base claim 35.

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claims 20-21, 27-29, 35-37 and 40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling only for an isolated peptide as set forth in claim 22 and a pharmaceutical composition comprising the peptide as set forth in claims 29 and 30 for inhibiting HARP induced angiogenesis, **does not** reasonably provide enablement for any peptide consisting of "an amino acid sequence at least 90% identical" to SEQ IDN NO: 2 or SEQ I DNO: 3 and exhibiting any angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG), any peptide differs from SEQ ID NO: 2 or SEQ ID NO: 3 by any conservative substitution of at least one amino acid, any pharmaceutical composition comprising any peptide mentioned above as set forth in claims 27-29, and a method for preparing a medicament as set forth in claims 35-37 and 40. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in **scope** with these claims.

Factors to be considered in determining whether undue experimentation is required to practice the claimed invention are summarized *In re Wands* (858 F2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). The factors most relevant to this rejection are the scope

of the claim, the amount of direction or guidance provided, the lack of sufficient working examples, the unpredictability in the art and the amount of experimentation required to enable one of skill in the art to practice the claimed invention. The specification disclosure is insufficient to enable one skilled in the art to practice the invention as broadly claimed without an undue amount of experimentation.

Claim 20 encompasses any isolated peptide consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3 or any fragment thereof, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG).

Claim 21 encompasses any isolated peptide differs from SEQ ID NO: 2 or SEQ ID NO: 3, by any conservative substitution of one or more amino acids and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG).

Claim 27 encompasses a pharmaceutical composition comprising any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) and at least one pharmaceutically acceptable excipient.

Claim 28 encompasses a pharmaceutical composition comprising any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 4 and exhibiting an angiogenesis inhibiting activity and a capacity for binding to anaplastic lymphoma kinase (ALK) receptor.

Claim 35 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) to a pharmaceutically acceptable vehicle.

Claim 36 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 4, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to anaplastic lymphoma kinase (ALK) receptor and a pharmaceutically acceptable vehicle.

Claim 37 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an

angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) and a second peptide consists of SEQ ID NO: 4 to a pharmaceutically acceptable vehicle.

Enablement is not commensurate in scope with how to make and use any peptide mentioned above and pharmaceutical composition comprising such peptides for the treatment that encompassed prevention of any pathology associated with angiogenesis, pathology associated with angiogenesis such as tumor, ocular lession, rheumatoid arthritis, or any skin disease.

The specification discloses only human HARP polypeptide comprising the amino acid sequence of SEQ ID NO: 1. The specification discloses three human HARP peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 that correspond to amino acid residues 13-39, 65-97, and 111-136 of SEQ ID NO: 1, respectively. The specification discloses SEQ ID NO: 2 and SEQ ID NO: 4, which correspond to amino acid residues 13-39 and 65-97 of SEQ ID NO: 1, that bind to glycoaminoglycans (GAG) and inhibit HARP mediated angiogenesis, see page 28. The specification discloses peptide of SEQ ID NO: 4 binds to the anaplastic lymphoma kinase "ALK" receptor and inhibits angiogenesis. The specification defines the term "similar" to encompass any sequences which are perfect resemblance or identity between the amino acids compared but also to the imperfect resemblance which is defined as similarity. This search for similarities in a polypeptide sequence takes into account the conservative substitutions which are substitutions of amino acids of the same class, but also include "variant, homologue or derivative amino acid sequence" which differ from the reference sequence by substitution, deletion and/or insertion of an amino acid or a plurality of amino acids, preferably a reduced number of amino acids, particularly by substitution of natural amino acids by non-natural amino acids or pseudo-amino acids at positions such that these modifications do not significantly undermine the biological activity of the peptides, see pages 7-8 of the specification.

The specification at page 17, lines 16-18 defines "treatment" to mean " treatment for a curative purpose (aimed at least at alleviating or stopping the development of the pathology) or a prophylactic purpose (aimed at reducing the risk of the pathology appearing).

The intended use of the peptide is for treatment or prevention of any angiogenesis associated pathology such as benign or malignant tumor including melanomas, carcinomas, sarcomas, rhabdomyosarcoma, retinoblastoma, neuroblastoma, and osteosarcoma. Amongst the solid tumors mention may be made in particular of tumors (primitive or not) of the breast, the ovary, the lung, the cervix, the digestive tract, in particular the colon, the urologic system, the

liver, the pancreas, the bones. Non-solid tumors are equally covered, namely in particular leukemia or lymphomas. The proliferative disorders can be treated at any stage in the proliferation. The peptides or the nucleic acids according to the invention are in particular useful for combating the development of tumoral metastases. Amongst the benign tumors mention may finally be made in particular of haemangiomas and hepatocellular adenomas, see page 15-16 of the specification.

At the time of filing, the specification does not teach how to make and use any peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2, 3 or 4 having the specific binding activity and maintains anti-angiogenic activity *in vivo* for treating or preventing any pathology associated with angiogenesis such as any and all tumor, any ocular lesion, rheumatoid arthritis, or any skin disease. Further, the specification does not teach how to make and use any derivative of peptide differs from SEQ ID NO: 2 or SEQ ID NO: 3 having any one or more conservative substitution and still having the specific binding activity to glycoaminoglycans and maintains anti-angiogenic activity in vivo for treating or preventing any pathology associated with angiogenesis such as any and all tumor, any ocular lesion, rheumatoid arthritis , or any skin disease. There is insufficient guidance as to which amino acid position within the sequence of amino acids of SEQ ID NO: 2, SEQ ID NO: 3 or SEQ ID NO: 4 to be substitute, deleted, added or combination thereof such that the resulting peptide having at least 10% difference to SEQ ID NO: 2, SEQ ID NO: 3, or SEQ ID NO: 4, respectively, still maintains binding to either glycoaminoglycans or ALK receptor and exhibiting anti-angiogenic activity *in vivo*.

The state of the art as evidenced by the teachings of the US Pat NO 6,103,880 (of record) are such that biologically active peptides having such an N-terminal sequence are all the more unexpected since it would be difficult for a person skilled in the art to predict that an addition of amino acids to the N-terminal sequence of the known peptide such as HARP family growth factor would improve its biological activity. The '880 patent teaches "in fact, predictions as to the effect of the addition, elimination or modification of amino acid in a given structure are impossible in the current state of knowledge of protein structures, even with the aid of the most advanced modeling technique" (see col. 3, lines 55-65, in particular).

Zhang et al (of record, J Biol Chem 274(9): 12959-12962, 1999; PTO 892) teach various human pleiotrophin (also known as PTN or HARP) peptides and peptide-containing residues 41-64 of PTN induces tumor transformation (see entire document, Discussion, in particular). Zhang et al teach NIH 3T3 cells expressing PTN 1-40 which contains the claimed peptide comprising

the amino acid residues 13-39 of HARP grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Likewise, NIH 3T3 cells expressing PTN 101-136 which contains the claimed peptide comprising residues 111-136 also grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Zhang et al teach it is unexpectedly that larger tumors were found at the sites of injection of NIH 3T3 cells expressing PTN peptide having deletion of the two internal repeats (residues 41-45 and 65-68), see page 12961, col. 1, in particular).

Further, the intended use of the peptide is for treating/preventing any tumor, any ocular lesion, rheumatoid arthritis, or any skin disease, let alone preventing any such diseases. At the time of filing, there is a lack of *in vivo* working example demonstrating any peptide consisting any sequence that is at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3 or any fragment thereof or any peptide having one or more conservative substitutions still binds to glycoamkinoglycans and maintaining angiogenic inhibiting activity. Likewise, there is insufficient guidance as to which one or more amino acid within the peptide of SEQ ID NO: 4 to be substituted conservatively, deleted, or added such that the peptide sequence having at least 90% identical to SEQ ID NO: 4 still maintains its 3-D structure, binds to ALK receptor and inhibits angiogenesis. There is no showing of any peptide mentioned above or any fragment thereof could treat any tumor, rheumatoid arthritis, or any and all skin disease, let alone preventing any tumor, rheumatoid arthritis, or any skin disease from happening. The term "*an* amino acid sequence" could be a full-length peptide of any peptide fragment thereof.

Pharmaceutical composition in the absence of *in vivo* data are unpredictable for the following reasons: (1) the protein may be inactivated before producing an effect, i.e. such as proteolytic degradation, immunological inactivation or due to an inherently short half-life of the protein; (2) the protein may not reach the target area because, i.e. the protein may not be able to cross the mucosa or the protein may be adsorbed by fluids, cells and tissues where the protein has no effect; and (3) other functional properties, known or unknown, may make the protein unsuitable for in vivo therapeutic use, i.e. such as adverse side effects prohibitive to the use of such treatment. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

Because the peptides mentioned above are not enabled, it follows that the method of preparing a medicament using any such peptide is not enabled.

Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

In re wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988), the decision of the court indicates that the more unpredictable the area is, the more specific enablement is necessary. In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification and the breadth of the claims, it would take an undue amount of experimentation for one skilled in the art to practice the claimed invention.

Applicants' arguments filed March 17, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the claims have been amended in such a way as to be directed to peptides consisting of a sequence at least 90% identical to SEQ ID NOs: 2, 3 or 4. In other words, the amended claims relate to peptides consisting of very specific fragments of the HARP factor, and comprising at most three differences compared to SEQ ID NOs: 2, 3 and 4.

It is respectfully submitted that the revised new claims pertain to a limited number of peptides, and that it would not amount to undue experimentation for the skilled artisan to practice the invention in view of the guidance in the disclosure and the knowledge in the art.

In this regard, it is well established that the test of enablement is whether one reasonably skilled in the art could make or use the invention based on the disclosure in the specification coupled with the knowledge in the art without undue experimentation. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In fact, the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides reasonable guidance with respect to the direction in which the experimentation should proceed. See, M.P.E.P. § 2164.01 and *In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

In the instant case, it is respectfully submitted that the disclosure provides sufficient guidance to enable the scope of the limited number of peptides of the new claims. Applicants wish to emphasize that the specification provides guidance, for example, from page 7, line 30 to

page 8, line 14, as to which specific mutations within SEQ ID NOs: 2, 3 and 4 are expected not to abolish the biological activity of the peptides. In addition, the specification contains a detailed description of several well-known methods for testing whether a peptide has the biological activity recited in the functional language of the claims. See, for instance, the disclosure from page 6, line 31 to page 7, line 20.

It is respectfully submitted that the skilled artisan, upon reading the disclosure and in view of the knowledge in the art, could construct any of the limited number of peptides encompassed by the new claims and then use the assays disclosed in the specification in order to confirm that such peptides have the requisite angiogenesis inhibiting activity and a capacity for binding to the ALK receptor. Moreover, such could be done using the routine techniques and procedures disclosed in the specification without undue experimentation.

Further, it is noted that the references relied upon by the Office as evidence of the alleged unpredictable nature of the art are not pertinent for the newly claimed peptides nor the rejections. In this regard, Zhang et al. teaches that peptides consisting of amino acids 1-40 and 101-136 of HARP have no angiogenesis inhibiting activity. In contrast, the present claims pertain to peptides consisting of sequences at least 90% identical to amino acids 13-39 and 111-136 of HARP. Further, as discussed in the disclosure (see for instance, page 4, line 23-25 of the original application), Applicants surprisingly found that such peptide fragments of HARP of the present invention are capable of inhibiting angiogenesis and tumor growth. Thus, it is respectfully submitted that such a teaching in Zhang et al. in no way negates this surprising finding by the Applicants. In other words, Zhang et al. does not demonstrate that the claimed peptides consisting of sequences at least 90% identical to amino acids 13-39 and 111-136 of HARP lack the requisite functional activity.

Similarly, US 6,103,880 does not teach any peptide consisting of sequences at least 90% identical to amino acids 13- 39 and 111-136 of HARP that does not exhibit angiogenesis inhibiting activity.

Therefore, the references relied upon by the Office in making the rejection do not negate the Applicants' surprising finding that the claimed peptide fragments contain the requisite functionality.

For these reasons, it is respectfully submitted that the skilled artisan, upon reading the disclosure and in view of the knowledge in the art, could construct any of the limited number of peptides encompassed by the new claims and then use the assays disclosed in the specification

in order to confirm that such peptides have the requisite angiogenesis inhibiting activity and a capacity for binding to the ALK receptor without undue experimentation. Therefore, withdrawal of the above-noted enablement rejection is solicited.

Contrary to applicants' assertion that the revised new claims pertain to a limited number of peptides, and that it would not amount to undue experimentation for the skilled artisan to practice the invention in view of the guidance in the disclosure and the knowledge in the art, Claim 20 encompasses any isolated peptide consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3 or any fragment thereof, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG).

Claim 21 encompasses any isolated peptide differs from SEQ ID NO: 2 or SEQ ID NO: 3, by any conservative substitution of one or more amino acids and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG).

Claim 27 encompasses a pharmaceutical composition comprising any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) and at least one pharmaceutically acceptable excipient.

Claim 28 encompasses a pharmaceutical composition comprising any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 4 and exhibiting an angiogenesis inhibiting activity and a capacity for binding to anaplastic lymphoma kinase (ALK) receptor.

Claim 35 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) to a pharmaceutically acceptable vehicle.

Claim 36 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 4, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to anaplastic lymphoma kinase (ALK) receptor and a pharmaceutically acceptable vehicle.

Claim 37 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) and a second peptide consists of SEQ ID NO: 4 to a pharmaceutically acceptable vehicle. Enablement is not commensurate in scope with how to make and use any peptide mentioned above and pharmaceutical composition comprising such peptides for the treatment that encompassed prevention of any pathology associated with angiogenesis, pathology associated with angiogenesis such as tumor, ocular lession, rheumatoid arthritis, or any skin disease.

At the time of filing, the specification discloses only three human HARP peptide consisting of the amino acid sequence selected from the group consisting of SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4 that correspond to amino acid residues 13-39, 65-97, and 111-136 of SEQ ID NO: 1, respectively. The specification enables reduces tumor growth using the specific peptide as set forth in SEQ ID NO: 2, 3 and 4. Other than the specific peptides, there is no guidance as to which amino acids within the peptide of SEQ ID NO: 2, 3 or 4 to be substituted, deleted, added or combination thereof such that the resulting peptide having 10% difference to SEQ ID NO: 2, 3 or 4 still inhibits angiogenesis in vivo. There is no showing of any modified peptide having at least 10% difference to SEQ ID NO: 2,3 or 4 or any modified peptide shorter than SEQ ID NO: 2, 3 or 4 still binds to glycoaminoglycans (GAG) or ALK receptor.

Ngo et al (The Protein Folding Problem and Tertiary Structure Prediction, pp. 491-495, 1994; PTO 892) teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) teach that even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and lost functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), resulting in losses biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and losses of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular). Mason *et al* further teach an equivalent protein such as TGFβ1 in which replacing cysteine residue for a serine residue resulted in loss bioactivity (See page 330, column 1, first paragraph, in particular).

Given the unlimited number of modified peptides, the actual biological activity of such peptide has yet to be demonstrated. Accordingly, treatment and/or prevention of any pathology associated with angiogenesis such as any tumor, ocular lesion, rheumatoid polyarthritis, or any and all skin disease using any modified peptide is highly unpredictable, varies depending on the animal model, means of administration and composition of the peptide. Accordingly, it would require undue experimentation of one skilled in the art to practice the claimed invention. See page 1338, footnote 7 of Ex parte Aggarwal, 23 USPQ2d 1334 (PTO Bd. Pat App. & Inter. 1992).

13. Claims 20-21, 27-29, 35-37 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention.

Claim 20 encompasses any isolated peptide consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3 or any fragment thereof, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG).

Claim 21 encompasses any isolated peptide differs from SEQ ID NO: 2 or SEQ ID NO: 3, by any conservative substitution of one or more amino acids and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG).

Claim 27 encompasses a pharmaceutical composition comprising any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) and at least one pharmaceutically acceptable excipient.

Claim 28 encompasses a pharmaceutical composition comprising any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 4 and exhibiting an angiogenesis inhibiting activity and a capacity for binding to anaplastic lymphoma kinase (ALK) receptor.

Claim 35 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) to a pharmaceutically acceptable vehicle.

Claim 36 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 4, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to anaplastic lymphoma kinase (ALK) receptor and a pharmaceutically acceptable vehicle.

Claim 37 encompasses a method for preparing a medicament for treatment of any pathology associated with angiogenesis comprising adding any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) and a second peptide consists of SEQ ID NO: 4 to a pharmaceutically acceptable vehicle.

At the time of filing, the specification discloses the reduction to practice of only a single species of peptide of SEQ ID NO: 2 within the claimed genus of peptide (at least 90% identical to SEQ ID NO: 2) and has the activity of inhibiting heparin binding growth factor (HARP) mediated angiogenesis and tumor growth and binds to glycoaminoglycans (GAG). The specification also discloses the reduction to practice a single species of peptide of SEQ ID NO: 3 within the claimed genus of peptide (at least 90% identical to SEQ ID NO: 3) and has the activity of inhibiting HARP mediated angiogenesis and tumor growth and binds to glycoaminoglycans (GAG). The specification also discloses the reduction to practice of a single species of peptide of SEQ ID NO: 4 within the claimed genus of peptide (at least 90% identical to SEQ ID NO: 4) and has the activity of inhibiting HARP mediated angiogenesis and tumor growth and binds to ALK receptor, see page 23-25.

The recitation of a peptide with at least 90% identity to SEQ ID NO: 2, 3 or 4 represents a partial structure. The claimed peptide share at least 90% sequence identity of the structure of SEQ ID NO: 2, 3 or 4, while 10% of the structure can vary. There is no teaching in the specification regarding which 10% of the structure can vary while retaining the ability of the peptide to binds to glycoaminoglycans (GAG) or ALK receptor and inhibits angiogenesis *in vivo*. Further, there is no art-recognizing correlation between any structure (other than SEQ ID NO: 2, 3 or 4) and the activity of binding to glycoaminoglycans (GAG) or ALK receptor and inhibiting angiogenesis induced by any growth factor.

The state of the art as evidenced by the teachings of the US Pat NO 6,103,880, of record, is such that biologically active peptides having such an N-terminal sequence are all the more unexpected since it would be difficult for a person skilled in the art to predict that an addition of

amino acids to the N-terminal sequence of the known peptide such as HARP family growth factor would improve its biological activity. The '880 patent teaches "in fact, predictions as to the effect of the addition, elimination or modification of amino acid in a given structure are impossible in the current state of knowledge of protein structures, even with the aid of the most advanced modeling technique" (see col. 3, lines 55-65, in particular).

Ngo et al (The Protein Folding Problem and Tertiary Structure Prediction, pp. 491-495, 1994; PTO 892) teach that the amino acid positions within the polypeptide/protein that can tolerate change such as conservative substitution or no substitution, addition or deletion which are critical to maintain the protein's structure/function will require guidance (See Ngo et al., 1994, The Protein Folding Problem and Tertiary Structure Prediction, pp. 492-495).

Mason *et al* (Molecular Endocrinology 8(3): 325-332, 1994; PTO 892) teach that even a single amino acid substitution from cysteine to alanine fails to maintain either the structure and lost functions such as intracellular assembly and secretion of the dimer protein (see page 327, column 1, in particular), resulting in losses biological activity (See activin cysteine mutant 4 and 12, page 327, column 2, in particular) and losses of receptor binding activity (See Receptor Binding Activities of activin cysteine mutant 4 and 12, page 327, column 2, in particular).

Zhang et al (of record, J Biol Chem 274(9): 12959-12962, 1999; PTO 892) teach various human pleiotrophin (also known as PTN or HARP) peptides and peptide-containing residues 41-64 of PTN induces tumor transformation (see entire document, Discussion, in particular). Zhang et al teach NIT 3T3 cells expressing PTN 1-40, which contains the claimed peptide comprising the amino acid residues 13-39 of HARP, grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Likewise, NIH 3T3 cells expressing PTN 101-136, which contains the claimed peptide comprising residues 111-136, also grew at a rate similar to that of the control cells (see page 12960, col. 2, in particular). Zhang et al teach it is unexpectedly that larger tumors were found at the sites of injection of NIH 3T3 cells expressing PTN peptide having deletion of the two internal repeats (residues 41-45 and 65-68), see page 12961, col. 1, in particular).

Although the disclose of SEQ ID NO: 2, 3 or 4 combined with the knowledge in the art, would put one in possession of proteins that are at least 90% identical to SEQ ID NO: 2, 3 or 4, respectively, the level of skill and acknowledge in the art is such that one of ordinary skill would not be able to identify without further testing which one of those peptide having at least 90%

identity to SEQ ID NO: 2, 3 or 4 or any one or more conservative substitution thereof (if any) have or maintain the claimed activities.

At the time of filing, Applicants are not in possession of any isolated peptide consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 3 or any fragment thereof, and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) or any isolated peptide differs from SEQ ID NO: 2 or SEQ ID NO: 3, by any conservative substitution of one or more amino acids and exhibiting an angiogenesis inhibiting activity and a capacity for binding to glycoaminoglycans (GAG) or any isolated peptide consisting of any amino acid sequence at least 90% identical to SEQ ID NO: 4 and exhibiting an angiogenesis inhibiting activity and a capacity for binding to anaplastic lymphoma kinase (ALK) receptor as well any pharmaceutical composition comprising such peptide for treating or preventing any pathology associated with angiogenesis for treating or preventing any angiogenesis associated pathology such as the ones recited in claim 40.

With the exception of the specific peptides consisting of SEQ ID NO: 2, 3 and 4, there is insufficient written description of sufficient relevant identifying characteristics i.e., complete structure, partial structure, physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure in any peptide as set forth in claims 20-21, 27-29, 35-37 and 40.

The specification discloses only one peptide from three different regions of human HARP factor comprising SEQ ID NO: 1 that inhibits angiogenesis mediated by HARP molecule. Because the described peptide of SEQ ID NO: 2, 3 and 4 is not representative of the entire claimed genus, and the specification does not disclose structural features shared by members of the genus of peptide at least 90% identical to SEQ ID NO: 2, 3 or 4, respective. Further, the term "a peptide consisting *an* amino acid sequence at least 90% identical to SEQ ID NO: 2 or SEQ ID NO: 2" encompasses any peptide shorter than SEQ ID NO: 2 or SEQ ID NO: 3. At the time of filing, there is not a single fragment of SEQ ID NO: 2, 3 or 4 has the claimed activity, in turn, effective to inhibit angiogenesis.

Accordingly, one of skill in the art would conclude that applicant was not in procession of the claimed genus because a description of only a single peptide of SEQ ID NO: 2, 3 or 4 is not a representative of the variant of peptide consisting of an amino acid sequence at least 90% identical to SEQ ID NO: 2, 3 or 4 or fragment thereof to show that the applicant would have been in possession of the claimed genus as a whole at the time of filing. Therefore, the specification

fails to satisfy the written description requirement of 35 U.S.C. 112, first paragraph, with respect to the full scope of claims 20-21, 27-29, 35-37 and 40.

Applicant is reminded that Vas-Cath makes clear that the written description provision of 35 U.S.C. § 112 is severable from its enablement provision (see page 1115). Applicant is directed to the Final Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001 and revision of training material on the Written Description Training materials, posed April 11, 2008 http://www.USPTO.gov/web/menu/written.pdf.

Applicants' arguments filed March 17, 2008 have been fully considered but are not found persuasive.

Applicants' position is that the Office has acknowledged that the specification clearly discloses isolated peptides consisting of SEQ ID NO: 2 or SEQ ID NO: 3, and compositions comprising the isolated peptide consisting of SEQ ID NO: 2, and SEQ ID NO: 3, or SEQ ID NO: 2, SEQ ID NO: 3 and SEQ ID NO: 4.

It is respectfully submitted that such peptides constitute a reduction practice, a disclosure of a representative number of species and a clear reduction to drawings/chemical formulas of the invention.

Further, as noted above, the new claims are directed to peptides consisting of a sequence at least 90% identical to SEQ ID NOs: 2, 3 or 4. As such, the new claims relate to peptides consisting of a limited number of specific fragments of the HARP factor, and comprising at most three differences compared to SEQ ID NOs: 2, 3 and 4. The specification at page 7, line 30 to page 8, line 14 also discusses which mutations within SEQ ID NOs: 2, 3 and 4 are expected not to abolish the biological activity of the peptides. It is respectfully submitted that this constitutes a sufficient disclosure of relevant identifying characteristics, such as structure or other physical and/or chemical properties, to sufficiently describe the claimed invention in full, clear, concise and exact terms. It also amounts to a sufficient disclosure of functional characteristics coupled with a known or disclosed correlation between function and structure. In view of the above, one of skill in the art would reasonably believe that Applicants were in possession of the claimed invention at the time of filing. Therefore, withdrawal of the above written description rejection is solicited.

14. Claims 22 and 30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

15. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, THIS ACTION IS MADE FINAL. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh, Ph.D. whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Eileen B O'Hara can be reached on (571) 272-0878. The IFW official Fax number is (571) 273-8300.

17. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Phuong Huynh/
Primary Examiner, Art Unit 1644
July 18, 2008